

inheritance we must utilize every avenue of approach at our command both direct and indirect. Information secured from animal experimentation can certainly serve as a light by which we can better see our way in our investigations in human genetics.

I. Domestication of the Norway Rat and its Implication for the Study of Genetics in Man^{1, 2, 3}

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PRIMITIVE man did not know about social security, old age pensions, unemployment insurance, and the many other devices that protect us, as members of an organized society, from stress of all kinds.

I bring this up because I want to consider with you today the genetics of structural and functional changes that may have occurred, specifically in the adrenal glands and sex glands during the course of man's adaptation from his primitive unprotected environment to the highly protected environment of our modern civilization. I want to postulate that changes in the adrenal cortex may account for the increasing incidence of such hypersensitivity diseases as rheumatoid arthritis, asthma, and perhaps some forms of mental illness, and that changes in the gonadal secretions may account in part for the present day high incidence of certain neoplastic diseases.

Primitive man lived in an environment in which physical strength, endurance and aggressiveness were at a premium. He had to fight for his food, shelter and mates and to protect himself against attack from enemies of all kinds, human and animal, as well as from the elements. In order to survive he had to remain constantly on the alert, ready either to defend himself or to flee. In this environment the strongest, most aggressive individuals survived—the weak and defective were quickly eliminated.

With the growth of community life, the environment changed in the direction of protection, cooperation, and less constant stress. The qualities needed in the primitive state were no longer at a premium. Less fierce, less aggressive individuals could survive. The capacity to "adjust" to others became increasingly valuable.

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An attempt to determine the physiological changes in man that paralleled this social development faces many difficulties. It is not possible even to make anatomical comparisons between primitive and modern man except between the so-called "hard" parts—the skeleton and teeth.

A more hopeful source of study, therefore, would seem to be animals that likewise have undergone the change from the stresses of the wild state to the security of a protected and controlled environment: in short, animals that have become domesticated.

Not all domesticated animals can be used for this purpose. In most instances the ancestral forms either are not specifically known or have been long extinct, leaving only paleontological and pictorial records of the teeth, skeleton and hair coat.

Of all animals, the Norway rat, the first animal domesticated for scientific purposes,⁴ is an outstanding subject in which to follow the structural and functional changes that occur during the process of domestication, changes that may indicate how the progress of civilization has affected man. It has the following advantages:

First, live wild Norway rats are readily available in large numbers literally at our door-steps, and equally large numbers of domesticated rats are available in laboratories throughout the world. Thus, comparisons of every type—anatomical, physiological and behavioral—can be made.

Second, since the domesticated Norway has been used in almost every field of biological research, we probably know more about it than any other animal except man. It is of special interest that much of our knowledge of adrenal and gonad histology and physiology comes from work on this animal, and that it has also been the favorite animal for studies on stress.

Third, though wild and domesticated Norway rats will breed with one another, neither breeds with any other rat, not even with the Alexandrine, the next most common rat in the world.

Fourth, the comparatively early age at which the rat matures makes it possible to follow the inheritance of various characteristics throughout many generations within a few years' time.

Finally, the Norway rat is similar to man in various ways, particularly in dietary needs, geographic distribution, world population, and colony formation.⁵

⁴ When, where and under what circumstances, the Norway first made its appearance in a scientific laboratory is not known. We do know that as early as 1856 a French physician, Philipeaux, used rats for his experiments on the adrenal glands.

⁵ The only other animal that even begins to offer the same opportunity for this type of study is the rabbit *Oryctolagus cuniculus* which has been widely used for food and fur and whose ancestors are still living in the wild state in Europe. Nachtshiem has given an excellent account of this animal's domestication in his book "Vom Wildtier zum Haustier." In many ways the Norway rat and the rabbit have undergone the same changes during the process of becoming domesticated. Eickhoff (1949) has used this rabbit for his important studies on the part played by the thyroid in reactions to stress.

In my laboratory we have used over ten-thousand wild rats during the past 10 years for studies in the fields of nutrition, endocrinology, toxicology and rodent control. Simple, effective methods have been devised for trapping, housing and handling these rats. (Emlen, 1944; Richter and Emlen, 1946)

The most important of these devices is a holder, designed by Dr. John Emlen, (1944) by means of which we are able to remove wild rats from their cages, weigh, inject, tube-feed them; and return them to their cages—all without the use of an anesthetic or any danger of being bitten and at the same rate that these procedures can be carried out on domesticated rats. We also use this device in holding and etherizing wild rats for operative procedures.

The wild Norway rat, like primitive man, lives in an environment in which it must constantly be on the alert and often has to fight for its very existence. It has to defend itself against all kinds of enemies, other rats, dogs, cats, owls, and snakes, as well as against man. It is a fierce, aggressive, suspicious animal that attacks at the least provocation and in captivity takes advantage of every opportunity to escape, remains suspicious and tense, and breeds poorly.

In marked contrast, the healthy domesticated Norway is tame, gentle, trusting; does not bite unless frightened or hurt, and makes no attempt to escape. It lives placidly in the controlled environment of the laboratory where food, water, shelter and safety are constantly assured. Its only contributions to its own survival are that it feeds, waters, and grooms itself, and that unlike the captive wild rat, it mates freely, reproducing at an early age and at a rapid rate. Like other domesticated animals it has shown numerous mutations. Castle (1947) has recently listed 23 strains that breed true.

We have sought to determine precisely the ways in which the domesticated Norway in the laboratory differs from its wild ancestor. Comparisons have been made between domesticated rats from our colony, which has been in existence for over thirty years, and wild rats. Our original albino stock came from the Wistar colony; a few piebald and hooded rats from the colony of Dr. E. V. McCollum were introduced about 27 years ago. Since then no new strains have been introduced. In physiological responses as well as in the weights of the various organs and glands, our rats are very like those of other laboratory colonies, so it is likely that they are representative of domesticated rats in general.

Our domesticated rats have been maintained under essentially the same environmental conditions throughout. The rats are fed a stock diet⁶ which maintains good health and reproduction. The temperature of the room is kept as constant as possible without air-conditioning, averaging 77° and fluctuating between 75° and 85°, except on a few very hot days in the summer when it occasionally reaches 90° or above. The laboratory is artificially lighted during

⁶ Graham flour 72.5%, casein 10%, skim milk powder 10%, butter 5%, calcium carbonate 1.5%, and sodium chloride 1.0%.

the daytime and always darkened at night. Care is taken to minimize all disturbing noises or changes. The breeding rats are handled individually about once each week when the cages are cleaned and changed.

No effort has been made to breed the rats for any special characteristics, except over a short interval of 2 to 3 years when female rats that proved to be unusually active in the activity cages (revolving drums) were regularly returned to the breeding colony. At no time during the 2 to 3 year period did they constitute more than 20 per cent of the breeding females. It is possible that some unconscious selection of less fierce, more tractable rats was practiced.

The wild rats were trapped in the city of Baltimore or on outlying farms, and were used either within a few days or after weeks or months in the laboratory; some were bred and their offspring studied, others were shot in the wild state (on farms) and autopsied within minutes.

The experiments and observations that I am about to describe were carried on over a 10 year period in collaboration with Susan Baker, Miguel Covian, Sally Dieke, John Emlen, William Griffiths, Charles Hall, David Mosier, John Neustadt, Katherine Rice, Philip Rogers, Eberhardt Uhlenhuth, Henry Wagner, David Wood, and James Woods.

Now as to our results. We have not yet discovered any differences in the skeleton or teeth, except that the domesticated rats are in general smaller at maturity. Comparison of the organ weights of the two strains does however show very significant differences. Some organs have become smaller during the process of domestication, some larger, others develop earlier in the domesticated animal. A more detailed account of these changes was presented in an earlier report. (Richter, 1949)

It is of particular interest that during the process of domestication the adrenal glands have become much smaller while the gonads and secondary sex organs develop at an earlier age in the domesticated than in the wild rats. It is also of interest that the pituitary is larger in the domesticated rats.

A number of other differences in structure and physiology have been found but I shall limit further discussion to the adrenals and gonads.

The adrenals are of special interest for the present discussion because of the vital part played by their hormonal secretions in the reaction of animals to stress. They secrete hormones that aid animals in meeting stress. It has been shown that the secretion of adrenal steroids in the rat is closely paralleled by the amounts of cholesterol and of ascorbic acid in the adrenal cortex, as well as by the amount of stored lipids, as demonstrated by staining with Sudan IV or osmic acid. Sayers and Sayers (1949) have fully reviewed this evidence. Thus, by measuring the concentration of cholesterol or ascorbic acid or stored lipids under various conditions, we have available a measure of the animal's reaction to a specific stressful situation. Evaluation of changes in the amounts

of lipids as indicated by various dyes gives an equally good indication of reaction to stress.

The adrenals are of interest also because of the important part that they play in metabolic regulation. Thus, the retention-excretion ratio of sodium chloride, and consequently, body water retention, is related to the concentration of circulatory steroids from the glomerulosa layer of the cortex. When domesticated rats are fed diets with a low salt content, this layer shows considerable activity, presumably secreting DCA or a similar compound that helps to conserve salt; on the contrary, when kept on diets high in salt this layer becomes depleted of lipids—and presumably secretes little or no hormones. (Greep and Deane, 1949).

Our studies, in confirmation of observations made by Watson (1907) and by Donaldson (1928) showed that the adrenals of domesticated rats have undergone a marked atrophy. They weigh $\frac{1}{2}$ to $\frac{1}{5}$ as much as in the wild rats of the same weight. A decrease in cortical tissue accounts for the entire difference. (Rogers and Richter, 1948) However, not all zones of the cortex have atrophied. Mosier has shown (1952) that the capsule is wider in the domesticated than in the wild rat; the fasciculata and reticularis layers are much narrower. The wild rat lacks a definite transition zone between the glomerulosa and fasciculata layers and there are other marked differences in the cytology of the various layers. Except for the glomerulosa layer these differences need not be discussed further.

The adrenals of domesticated rats have decreased not only in size but in their content of cholesterol and ascorbic acid and of the various lipids that stain with Sudan IV, Sudan black and other similar dyes. Nichols (1950), Wood (1952), and Mosier (1952). Sudan IV stained sections of the adrenals of domesticated rats show only a sparse deposition of lipid in the fasciculata zone and even smaller amounts in the glomerulosa and reticularis zones, as compared with the wild rat.

We have learned, further, that the two strains of rats react very differently to all stress producing situations: confinement in a cold room at 2°C, fighting other rats, injections with 'DCA, irradiation, and starvation; likewise to injections with ACTH. In these studies the rats were killed by shooting and the adrenals were removed within seconds.

In the first of these series of experiments rats were kept in a cold room at 2°C for three hours. Some were killed immediately after being removed; others at intervals up to 24 hours. The domesticated rat's adrenals lost most of their lipid; the wild rat's none at all.

Fighting brought out much the same difference. For these experiments we used our so-called 'fighting chamber'—a box 12 x 12 x 18 inches, equipped with a glass front and a floor made of iron rods, spaced $\frac{3}{4}$ inches apart and

alternately wired to the two poles of an induction coil. Two wild rats placed in this chamber will start fighting almost at once after receiving only a mild shock, each one apparently suspecting the other of having inflicted the pain. An occasional shock suffices to keep the rats fighting. Pairs of domesticated rats do not fight. They spend their time in trying to escape. However, a domesticated rat can be forced to fight by placing it in the chamber with a wild rat. It will defend itself against the attacks of the wild rat. In our experiments the rats were fought for 10, 20 or 30 minutes, and killed either at once or at various intervals after being removed from the chamber. In all domesticated rats, even those killed after the short fighting periods, the adrenal lipid became very sparse or disappeared altogether in all zones. In contrast the wild rat's adrenals showed no loss of lipid even after the rats had been fought for 20 to 30 minutes. In some instances the amounts of lipid actually seemed to be increased.

Injection with DCA gave very similar results.

Irradiation with 400r depleted the lipids from the domesticated rat's adrenals in less than half an hour, but had no detectable effect on the lipids of the wild rat. Results of preliminary experiments indicate that domesticated rats are less able to stand irradiation since at their LD_{50} —720r—we have not killed any wild rats. (Dieke, unpublished)

Starving the rats for 24 hours likewise depleted the lipids from the adrenals of domesticated rats but not of wild rats.

It is of interest then that direct stimulation of the adrenals with ACTH even in amounts as large as 50 mg per animal, did not perceptibly reduce the large amount of lipid in the wild rat's adrenals, whereas in the domesticated rat is caused the disappearance of all except minute amounts.

The changes in ascorbic acid content of the adrenals produced by stress were measured by Woods (1952). He found that fighting, and other forms of stress, produced a great decrease in the case of domesticated rats but none at all in the wild rats.

In brief, the adrenals of the domesticated rats become depleted of lipid and ascorbic acid almost at once after even mild forms of stress; in marked contrast, the adrenals of wild rats do not lose any of their rich supply of lipid or ascorbic acid, even after very severe forms of stress. One possible explanation for these results would be that the wild rat's adrenals can produce hormones as fast as they are being depleted, whereas the domesticated rat's adrenals utilize them faster than they can be produced.

Adrenalectomy has a much less damaging effect in the domesticated rats. They survive adrenalectomy on only small amounts of salt in their diet, whereas wild rats do not survive when given salt in any amount or in any form. (Richter, Rogers and Hall, 1950) They do not survive with any consistency even when treated with cortisone or DCA or both. (Covian, 1949)

A further marked difference in adrenal physiology was brought out by experiments on the effects of feeding salt to the two strains. (Richter and Mosier, 1952) For a period of 70–80 days the rats received salt in their food in concentrations ranging from 2 to 35 per cent. Even in the lowest concentrations most of the domesticated rats lost all lipid from the glomerulosa layer of their adrenals; whereas the wild rats did not lose lipid from this layer even on the highest concentrations.

The results of these various experiments on the adrenal glands indicate that the domesticated rat is much more able to compensate for the loss of the adrenal secretions than is the wild rat. In other words, during the process of domestication the adrenal secretions have come to play a comparatively less important part.

We may now consider the changes that have simultaneously been occurring in the function of the sex glands. Domesticated rats mature earlier than do wild rats as indicated by an earlier opening of the vagina and by reproduction at an earlier age. Further, they mate freely at any time of the year, whereas wild rats mate usually only during the spring and fall, and then not nearly so freely as do domesticated rats at these times. Domesticated rats still retain some of this cyclical pattern since in our colony which is kept under fairly constant conditions, the rats are more active and tend to reproduce more readily in the spring and fall, but they do reproduce readily at all times. Domesticated rats are more fertile. In most colonies practically 100 per cent of females become pregnant when placed for 4 to 6 days with an active male. Many wild rats living in the cities apparently never become pregnant, since Davis and Emlen (1948) failed to find placental scars in a large number of captured wild females, many of them old enough to have had at least a year's opportunity to become pregnant.

A conclusive answer to the question of what changes have occurred in the function of the sex glands would be given by a quantitative study of sex activity of normal and gonadectomized domesticated and wild rats. The effects of gonadectomy would be of special interest, since from the degree of defect produced it should be possible to measure the relative importance of the roles played by the gonads—just as a comparison of the effect of adrenalectomy threw light on the function and relative importance of the adrenal secretion in the two strains. A direct comparison of sexual activity is not possible because the wild rats are loath to mate under observation.

Another means of comparing the importance of the gonadal secretion in the life of these two strains is open to us. This is the study of the effect produced by gonadectomy on spontaneous running activity as measured in revolving drums. Wang (1923) showed many years ago that in domesticated rats gonadectomy has a very profound secondary effect. These rats become very inactive

—about one-twentieth as active as they were before. They gain weight, even though they eat less.

It has now been found that in marked contrast wild Norway rats remain as active after gonadectomy as before; further, they do not gain weight, nor decrease their food intake as do the gonadectomized domesticated rats. (Richter and Uhlenhuth, 1952 A)

It was further found that gonadectomy likewise has little or no effect on activity, food intake and body weight of two other wild species, the Alexandrine rat and the cotton rat. (Richter and Uhlenhuth, 1952 B) Thus, it may prove that a failure of gonadectomy to produce any profound changes in these characteristics is typical for wild animals.

We were interested in finding an explanation for the great reduction in activity that gonadectomy produces in domesticated rats and its failure to produce any demonstrable change in activity of wild rats. It occurred to us that the wild rat might have an auxiliary source of androgens and estrogens—possibly in the adrenals. The finding that after gonadectomy the secondary sex organs were as small or even smaller in the wild than in the domesticated rats seemed to eliminate this explanation.

It occurred to us next that differences in the amounts or character of the adrenal secretions might account for the difference in the effect of gonadectomy. In other words, that the secretions from the larger and more active adrenals of the wild rats might help to keep them normally active after the gonadal secretions had been removed. To test this theory, treatment with cortisone, DCA or Compound S was started in domesticated rats immediately after gonadectomy. It was found that all three compounds prevented the sharp fall in activity, increase in body weight, decrease in food intake, and that cortisone and Compound S maintained the running activity at its preoperative levels.

Thus, the conclusion would seem justified that during the process of domestication adrenal hormones have become less important and gonadal secretions more important in the life of the Norway rat.

Experiments in progress at the present time indicate that wild and domesticated rats respond very differently to hypophysectomy—particularly so far as running activity is concerned. In earlier experiments it was found that hypophysectomy reduced the running activity of domesticated rats to a very low level, even lower than that found after gonadectomy. The wild rats appear to remain quite active after hypophysectomy, not as active as normally or after gonadectomy, but still far more active than the domesticated rats.

At this point I should like to recall to your attention the finding that the pituitary is larger in the domesticated than in the wild rat. This may mean that in the domesticated rat this gland has hypertrophied as a result of its effort to maintain the failing target organs, especially the adrenals. It may also mean that in the wild rats the target organs have a greater autonomy and need less

stimulation from the pituitary. In contradiction of the latter explanation is the fact that hypophysectomy produces very different effects on the adrenals in the two forms, as revealed by both histological and histochemical studies.

These many observations indicate that definite differences exist between the present day domesticated rat and its wild ancestor. Unfortunately, our knowledge of the course of these changes from the wild ancestor to the present day domesticated rat is still very limited. That such changes probably progressed gradually is likely from observations made by ourselves and others who have had colonies for any length of time. Over the course of years the rats become tamer, less fierce, and less apt to bite, or to attempt escape. The most valuable information on the probable progress of events in this interval comes from observations made by King and Donaldson, (1929), and King (1939) pioneer workers on domestication of the wild rat, in which they attempted to reproduce the entire domestication process under controlled conditions. They started with 6 wild rats and bred them through 25 generations. They found that in general from one generation to the next gradual changes in organ weights and behavior occurred, all of which were in the direction of the present day domesticated animal, but by the 25th generation had not yet reached the average levels of the domesticated rats.

We may now inquire into the possible stimuli which induced these changes and consider the environmental and genetic factors concerned. Environmental factors would include the effects of eating the stock diet over long periods of time; living in a room with a fairly constant temperature; being handled at regular intervals by laboratory helpers. For instance, the daily ingestion of large amounts of salt from weaning might have a consistently depressant (but not genetic) effect on the adrenals of each generation. If this dietary factor were the only cause involved, the effect should also gradually disappear when the rats are put on another diet.

Other environmental factors to be considered are those acting on the rats during their lifetime to produce behavioral differences, such as differences in the life experiences of the wild rat and the domesticated rat. To analyze these differences it will be necessary to obtain baby rats from the field or first generation offspring born in the laboratory to captured pregnant wild rats and raise them with a control group of domesticated rats, all the while maintaining identical conditions of diet, temperature and handling. Some studies have already been made on such first generation captive wild rats. We know that they grow up to be less suspicious, less fierce, and more tractable than their parents, though they are still very excitable, bite readily, and will make use of any opportunity to escape.

Similarly, it would be profitable to study the effects produced on organ weights and behavior by placing domesticated rats in the environment of the wild rat in city blocks and farms. Recapturing them at a later date and studying

any changes produced should add to our knowledge of the effects of lifetime environmental influence.

Both of these suggested experiments to control the environment could also serve to isolate the genetic factors of the two strains of Norway rat. Cross-breeding experiments may also be used for this purpose. It has been found that the weights of the adrenals and preputials of the hybrids tend toward those of domesticated rats. The most conclusive evidence will come from experiments in which fertilized eggs from wild rats are implanted into domesticated females and vice versa.

Of special interest from the point of view of genetics is that the number of fungiform papillae on the tongues of domesticated rats is definitely smaller—for domesticated rats 178.3 as compared to 212.9 for wild rats. (Richter and Fish, 1946) We have here an opportunity to put a genetic study on a numerical basis.

Selection seems to have played the most important part in the production of the differences between these two strains. By selection we mean here not the natural selection of wild rats in their natural habitat where the wildest, fiercest, and strongest—the fittest for the environment—survive, but selection in the artificial environment of the laboratory, where the fittest for this type of environment survive—those that are most tame, gentle and fertile. The two life stages in which this selection process has the most effect are during mating and nursing. In captivity wild rats do not mate well. In only a few out of many instances when rats are put together does a pregnancy result. In each instance it is likely that it is the tamest rats of any group that mate. This will be true of mating in each successive generation, so that the tamer rats will be more apt to propagate their own characteristics, including their presumably smaller adrenals. After the young are born, wild mothers frequently eat the entire litter, especially if they are disturbed, so that at this stage an even more severe screening for tameness occurs. The rats that do survive these two stages must be the least apprehensive and through successive generations should produce progressively tamer animals.

Thus we can think of three types of selection: (1) “natural” selection in the unprotected environment of the wild state; (2) controlled selection by man in captured or domesticated animals by breeding; (3) “natural” selection in a protected or artificial environment.

The results of these studies have given us a glimpse into the realm of changes that may occur in a large animal population when the animals are taken out of their free environment and placed in a controlled environment.

It may be asked now whether the knowledge obtained from this glimpse can be of any help in throwing light on what has happened or may still be happening to man during the process of his becoming domesticated or civilized.

We know that man, like the wild Norway rat, originally lived in an environ-

ment in which he had to search for his food, provide his own shelter, fight for his mates—an environment, in short, in which his fitness, hence his survival, was measured by his physical activity, aggressiveness, and ability to withstand violent change. But with the growth of communities and the consequent increase in daily peace and security for the individual, a new environment developed or may still be developing, in which man is largely protected from enemies, and his food, shelter, and livelihood are guaranteed. Man thus may have worked out a controlled environment for himself in which a transformation occurred, somewhat like that undergone by the Norway rat in its adaptation to colony life in the laboratory, resulting in an increase and perhaps even the predominance of the progeny of the so-called weaker, the milder, “better adjusted” individuals.

Here, just as in the domestication of the rat, a selection process—the selection of the “fittest” for this type of environment—must have played the most important part.

This process of domestication has gone quite far in our present day society. Man is now protected almost from the cradle to the grave with all kinds of devices—such as family welfare, social security, unemployment insurance, old age pensions, police protection.

The Romans of the Second Century apparently had achieved an even higher degree of social security and protection. According to Carcopino (1941)—the author of a most interesting book—“Daily Life in Ancient Rome”—80 to 90 per cent of the inhabitants at that time of the great capital city, Rome, depended for their livelihood on public funds—and everyone enjoyed at least one day of holiday for each day of work.

The ultimate in the direction of social security and with it control of man, toward which many people believe we are heading, has been described by Orwell in his book “1984”—a not too happy picture in which security has been developed to such a high degree that man’s every movement and even thoughts are observed and directed through a two way television arrangement. Orwell’s idea of man’s life in 1984 closely resembles that of our domesticated Norway rat—“happily” living out its caged existence.

It is clear that man has undergone great changes in behavior during the long years of domestication. We do not know, however, what anatomical and physiological changes have occurred—especially in his adrenal and sex glands. It has not been possible to make comparisons of adrenal weights, the ascorbic acid and lipid content, or of weights and histology of the gonads, in typical representatives of primitive man and modern man.

There are, however, indirect indications that marked changes may have occurred in these glands. At the present time it has been estimated that over 12 million individuals in this country suffer from hypersensitivity diseases, rheumatoid arthritis, asthma, and some mental diseases—all of which may have their origin in deficient functions of the adrenal glands since they respond so

remarkably to treatment with cortisone and ACTH. That a permanent deficiency underlies these diseases is known from the fact that treatment with cortisone and ACTH gives relief only so long as it is continued.

Similarly we know that many individuals suffer today from neoplastic diseases—some of which apparently have their origin in or are greatly influenced by a hyperactivity of the gonads since reduction or elimination of the gonadal secretion through castration so remarkably arrests the growth of these neoplasms and treatment with sex hormones greatly accelerates their growth.

It would be of interest to know whether these two groups of diseases likewise were so prevalent at the height of the Egyptian and Roman civilization.

Should it turn out that changes in these glands have actually paralleled man's integration into highly organized societies, we would want to know what can be done about it. How can we correct these undesirable secondary effects? Certainly this would be a problem for the human geneticist as well as for the sociologist and psychiatrist. We might get help, however, from observations on the anatomy, physiology and behavior of domesticated Norway rats that have been returned to the wild environment. Do the adrenals and gonads of such animals regain weight levels of wild rats? And if so in how many generations? Or will it be necessary to reevaluate the advantages and disadvantages of the high degree of protection that we all enjoy in our present day society?

Thus, in summary, the Norway rat, the first animal to be domesticated for experimental purposes, has during the course of that domestication, during its transition from the free environment of its wild habitat to the controlled conditions in the laboratory, undergone marked anatomical, physiological, and behavioral changes. The adrenals have come to play a less important part in its life; the gonads a more important part. The observations of these changes may help us to understand some of the changes that have occurred in man during his transition from this original free environment to the highly protected and controlled environment of modern society.

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2. Humoral and Cellular Elements in Natural and Acquired Resistance to Typhoid^{1,2}

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SIXTY years ago investigators, beginning with Flugge, Nuttall, Buchner, and Ehrlich, had developed a humoral theory of resistance whereby the blood

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